Concise Syntheses of GB22, GB13, and Himgaline by Cross-Coupling and Complete Reduction

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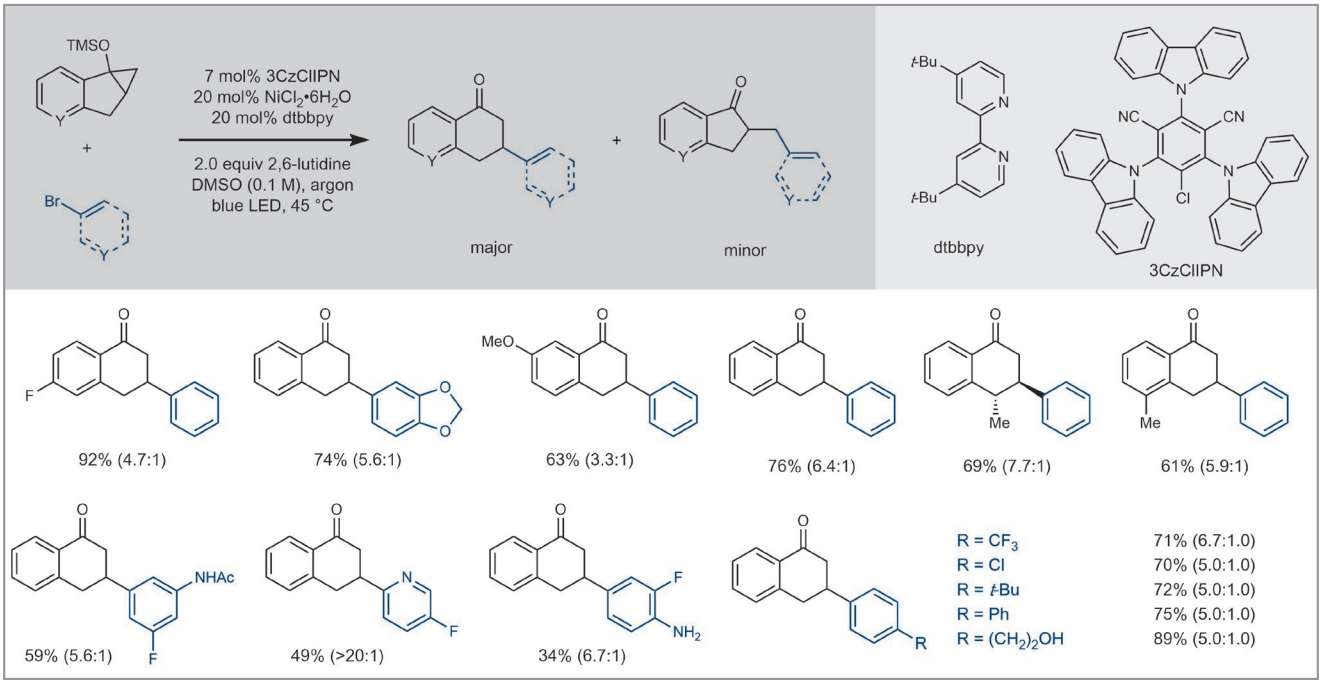
Galbulimima (GB) is a genus of large, flowering tree that grows in tropical regions of eastern Asia and Oceania. GB bark finds use as an antipyretic, analgesic, and hallucinogenic by indigenous Papuans, although the alkaloid or alkaloids responsible for these responses remain unknown. The group of Professor Ryan Shenvi at Scripps Research (La Jolla, USA) has been working on this problem. Professor Shenvi explained, "Due to the poor accessibility of GB trees, low natural abundance of alkaloids, and considerable variation between bark samples, chemical synthesis may be the best way to correlate alkaloid structure to biological function." Access to class III GB alkaloids was significantly enhanced by strategic installation of methine stereocenters and a novel metallaphotoredox cross-coupling of aryl bromides and siloxycyclopropanes (Scheme 1).

Eleanor Landwehr, one of the first authors on this *Science* paper, told SYNFORM: "I joined this project during pandemic shutdowns and shiftwork, so it has been an adventure from the start. Initial photochemical conditions relied on a cooling fan and ventilated box, resulting in variation from reaction to reaction, which contributed to irreproducibility." Ms. Landwehr and author Dr. Meghan Baker worked diligently to optimize the photochemical reaction and explore its applicability to a variety of substrates. "Application to the pyridine siloxycyclopropane and aryl bromide necessary for GB alkaloid synthesis, however, resulted in low yields," said Dr. Landwehr. She continued: "It was also difficult to access large quantities of the pyridine siloxycyclopropane. I was able to simultaneously develop an alternative Suzuki/Kulinkovich route to the pyridine siloxycyclopropane with visiting student Leo Smith and optimize this cross-coupling to 57% isolated yield."

The challenging Friedel–Crafts reaction was solved by author Dr. Takuya Oguma, who found that the reaction proceeded cleanly when substrate was added to a mixture of HFIP and Et_2AlCl (Scheme 2). Ms. Landwehr explained: "In the presence of other strong Brønsted or Lewis acids, an unexpected



Scheme 1 A new *endo*-selective cyclopropane cross-coupling was developed to access attached-ring motifs that are inaccessible by enone conjugate addition.

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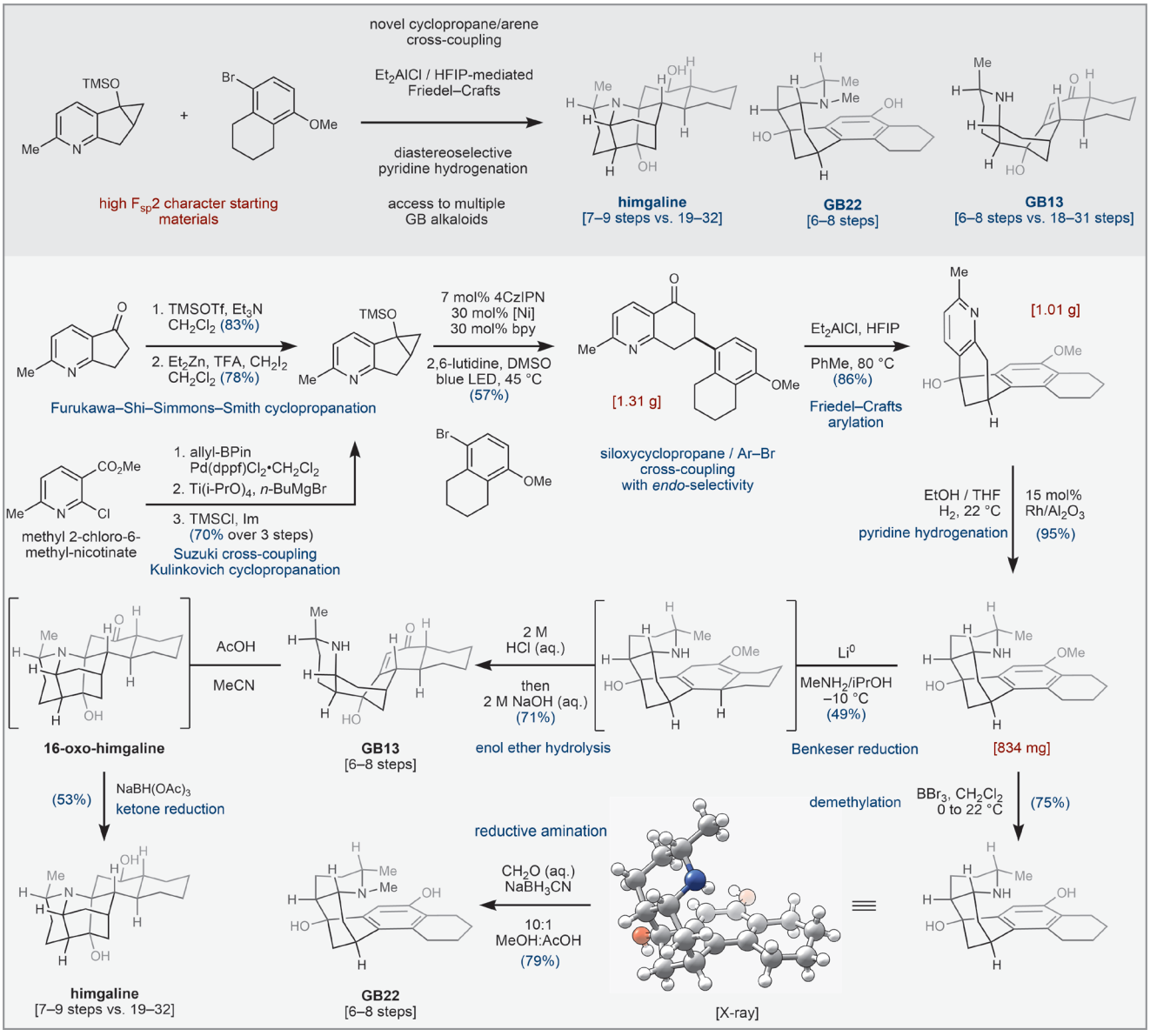
retro-Friedel–Crafts reaction cleaved our hard-won attached-ring bond."

On the cusp of her thesis defense, Meghan Baker discovered that methylamine solvent enabled efficient arene reduction, beyond the trace quantities observed with other conditions. "Prior to this observation, we could not decide whether to publish the substrate scope and GB22 or to add GB13 and himgaline to the same manuscript," remarked Ms. Landwehr. She continued: "Her contribution compelled us to include these more complex natural products. Ryan was so excited by the discovery that he joined us in lab for a few days and even made some of our first crude mixtures of GB13 and himgaline. For the first months of optimization, we were able to use an old lecture bottle of methylamine. This became a game of chicken between yield and residual gas: we feared for the day that this US Drug Enforcement Administration (DEA)-regulated substance would run out and we would be stuck. The day finally came when, in the middle of a Benkeser reduction, the lecture bottle petered out. That day we were forced to jury-rig a system to free-base an old container of methyl-



Scheme 2 Aromatic building blocks can be advanced to high fraction sp^3 *Galbulimima* (GB) alkaloids through a sequence of simple stereoselective reductions.

amine hydrochloride with NaOH, pass the gas through a drying tube and condense it into the reaction vessel."

This slow setup significantly impeded optimization. So, the discovery that a Birch variant reported by Koide *et al.* efficiently reduced the same arene was a great relief. Ms. Landwehr said: "I remember vividly my lab mate Nathan Dao running up to me and saying, "Did you see the Birch reduction in *Science* today?" and within 30 minutes the first LC showed mostly our desired product."

Acid hydrolysis of the enol ether followed by basification with sodium hydroxide yielded GB13 with only small amounts of the minor diastereomer. Ms. Landwehr said: "Stereoselectivity may arise from conversion into 16-oxo-himgaline upon treatment with acid, followed by equilibration to the lowest energy configuration."

Professor Shenvi concluded: "If targets are chosen carefully, total synthesis can be an irreplaceable and enabling science. Preliminary data already indicates that high-affinity biomolecular targets for class III alkaloids are found among human neuronal receptors. We expect other alkaloids from the bark of *Galbulimima* to yield a trove of new leads for therapeutic development."

About the authors

Top row, left to right: M. A. Baker, Prof. R. A. Shenvi, E. M. Landwehr; Bottom row, left to right: T. Kawajiri, T. Oguma

Meghan A. Baker received her B.S. in biochemistry from the University of Texas at Austin (USA) in 2016 and completed her Ph.D. in the lab of Professor Ryan Shenvi at Scripps Research (USA) in 2021. She is now a Senior Scientist in Discovery Process Chemistry at Merck in South San Francisco (USA).

Ryan A. Shenvi earned his PhD in 2008 as an NDSEG predoctoral fellow with Professor Phil Baran at the Scripps Research Institute (USA). After NIH-funded postdoctoral studies with E. J. Corey at Harvard University (USA), Ryan returned to Scripps to start his own research group. His laboratory develops new chemistry to navigate natural product space and interfaces synthesis design with structural biology.

Eleanor M. Landwehr earned her B.S. in chemical engineering from UW-Madison (USA) in 2020 where she conducted research in the lab of Jennifer Schomaker. She is currently a second-year student in the Skaggs Graduate School of Chemical and Biological Sciences at Scripps Research (USA).

Takuya Oguma is an associate director at Shionogi & Co. Ltd. He earned his PhD in 2014 at Kyushu University (Japan), where he explored iron-catalyzed asymmetric oxidation with Dr. Tsutomu Katsuki. He joined the research group of R. A. Shenvi at Scripps Research (USA) as a visiting scientist and developed methodology and total synthesis (2018–2019). He is currently focusing on CNS drug discovery at Shionogi (Japan).

Takahiro Kawajiri received his B.S. (2016) and Ph.D. (2020) in the lab of Professor Hironao Sajiki at Gifu Pharmaceutical University (Japan). He joined the lab of Professor Ryan Shenvi at Scripps Research (USA) in 2018 as a visiting student. He is currently a process chemist at Shionogi (Japan).

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